REMARKS

Claims 18-48 are now active in the present application. Support for these claims is found in Claims 1-17 and the specification as originally filed.

Applicants wish to thank Examiner's Marvich and Ketter for the courteous discussion granted to the Applicants' undersigned representative on October 23, 2002. During this discussion, the Applicants' representative pointed out the differences between the present invention and the Georges publication. In particular, it was noted that since Georges describes selectively killing the donor CTL with gangcylovir, the TK gene is actually transferred into the donor specific cells but not the recipient specific cells as in the present claims (see, for example, the Abstract: "Conclusions"[1] and the discussion on page 542, column 2, paragraph 12). In addition, the use of the TK gene as a mediator of cell death can not be considered to be therapeutic, i.e., that which provides a positive medical or physiological benefit. Therefore, the description in Georges is not the same as the invention as claimed, which provides stimulating a T cell of a graft recipient *in vitro* to yield a graft recipient-specific T cell; and transfecting **the graft recipient-specific T cell with a therapeutic gene** (as in Claim 18).

During the discussion, the Examiner suggested we amend the claims to more clearly define the transfection of the therapeutic gene into the recipient specific T cell, which is now reflected in the new claims submitted herein. Accordingly, withdrawal of the rejection under 35 U.S.C. § 102(b) over Georges et al is requested.

During the above-noted discussion, the Applicants' representative also explained why the present claims are, in fact, enabled by the specification and the common knowledge in the

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1 "We have demonstrated efficient ex vivo transduction, expansion, maintenance of alloreactivity, and gancyclovir-mediated ablation of canine CTL. . ."

2 "This shows that Hs-tk-transduced CTL were specifically killed with ganciclovir, without the emergence of ganciclovir-resistant T cells."

art and pointed to publications available at the time of filing for support. A detailed description of those references as well as the references themselves are filed herewith in the form of a Declaration under 37 CFR § 1.132 executed by one of the named Inventors, Dr. Thomas Ritter. Also presented in the Declaration are data demonstrating that the "inhibitory effect of vIL-10 could be blocked by the addition of a neutralizing antibody directed against vIL-10 showing the specificity of the inhibitory effect of vIL-10 on the production of TNF-α"

Briefly, Dr. Ritter summarizes the relevant state of the art and as result concludes that the invention as claimed is fully enabled by this knowledge in light of the specification as filed. Dr. Ritter points out that retrovirally transduced cells do, in fact, are detectable over a long period of time3, but notwithstanding this knowledge, sustained expression is not the only factor to consider since immunomodulation in early stages of transplantation have been shown to be sufficient in inducing a stable tolerance.4

Dr. Ritter also addresses the efficiency of transduced allogenic cells, generally and notes on page 3 that the present claims are directed to ex vivo modified autologous cells from the patient and as a result "the efficiency of implantation would not be expected to pose the same problems that are associated with allogenic transplantation and treatment regimens."

Dr. Ritter further notes that "not all human transplants are established before therapy is begun, which is characteristic of cadaver-donor transplantations. There are numerous transplantations where this is not the case, for example, in living-donor transplantations." As a result, the in vitro modified T cells and there method of use have a significant practical use.

In addition, Dr. Ritter points to the data in the specification in Figures 1-3 and the vIL-10 data presented in the Declaration (see also Qin and De Waal Malefyt attached to the Declaration), which shows that the ex vivo transduced T cells exhibit essentially the same

3 See pages 2-3, item 7 in the attached Declaration.
4 See page 3, item 7, third paragraph.

phenotype as *in vivo* regulatory T-cells as it relates to the expression of immunoregulatory molecules.

Based on this evidence, Dr. Ritter, who has a Ph.D. in Biology and who has been employed as scientist for 7 and a half years, concludes that the invention claimed in this application can be made and used in transplantation treatment protocols.

In view of the above, Applicants request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Regarding the priority application, Applicants note that a request to amend the specification has already been filed on the date this application was filed in the Patent Office. Applicants direct the Examiner's attention to item 18 on the Utility Patent Application Transmittal filed with this application. Notwithstanding this initial request, Applicants are again requesting amendment to the specification to insert the priority application information on page 1. In addition, Applicants submit herewith a certified copy of the German Priority document 10028833.2 filed on June 9, 2000.

In the event the Examiner's requires clarification on any issue in this case, she is invited to contact the Applicants' undersigned representative to resolve the matter expediently.

Applicants submit that the present application is now ready for allowance. Early notification of such allowance is requested.

Respectfully submitted,

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